N-terminal portion of the molecule. In clinical trials with Protropin in growth hormone-deficient children, linear growth rates were comparable to those in children receiving pituitary-derived hGH. Of 84 children treated with Protropin, antibodies to the growth hormone developed in 40%, but this did not interfere with growth except in one child.

The primary indication for treatment with synthetic human growth hormone is growth hormone deficiency shown by subnormal growth hormone response to two provocative tests. Some very short children growing less than 4.5 cm per year but with normal growth hormone levels in response to provocative stimulation have also responded to the use of human growth hormone, but indications for treatment are not well defined. The possible risks and benefits of treatment with hGH in other children with short stature is not yet known.

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Current Therapy for Asthma—New Inhalants

INHALATION THERAPY has increased in importance for the treatment of asthma as more effective drugs have become available and newer methods and techniques of delivery have been developed.

Several new β-adrenergic bronchodilator aerosol drugs are available for the treatment of asthma. One of the first β_2-agonists developed for asthma was isoproterenol, which has a short duration of activity and both β_1- and β_2-specific effects. In a search for more selective and longer acting drugs, new agents have been developed by modifying the chemical structure of the basic catecholamine molecule. Isoetharine has a duration of activity similar to that of isoproterenol, but is more β_2-selective. Noncatecholamine inhalants were subsequently developed and include metaproterenol, albuterol, terbutaline and bitolterol. These agents have a somewhat slower onset of action but a much longer duration of activity and greater β_2-selectivity than isoproterenol. Terbutaline, albuterol and bitolterol may be somewhat more bronchoselective and have a longer duration of activity than metaproterenol.

Although the new β-agonists are safer than their predecessors, they can cause adverse effects. Adverse cardiac effects can also be intensified by the concomitant use of theophylline, which can stimulate endogenous catecholamine release. Large doses of inhaled adrenergic agents alone or with theophylline can lead to hypopotassemia, thus greatly increasing the chance of cardiac arrhythmias. Paradoxical increases in airway obstruction and aggravation of hypoxemia reported following isoproterenol sulfate inhalations has not been reported with the newer, more selective agents. Sulfites, used as antioxidants, are present in bronchodilator solutions and have recently been found to cause bronchoconstriction in some susceptible patients with asthma. These substances, however, are not present in metered-dose inhalers or in the individual-dose vials of metaproterenol sulfate solution. With respect to tachyphylaxis, it is felt that the more selective β-agonists can be used for prolonged periods of time without fear of reducing bronchodilator activity.

One third to one half of patients use an improper technique when using metered-dose inhalers, and about 14% to 16% are unable to learn even after careful instruction. A new technologic development uses a spacer attachment consisting of a tube, cone or holding chamber between the actuator of the metered-dose inhaler and the patient's mouth. These devices not only improve delivery of the medication to the lungs and decrease oropharyngeal deposition but, of greatest importance, overcome the need for synchronization between firing the aerosol and inhaling. Large-volume spacers or reservoirs (500 to 1,500 cm) equipped with valves are particularly valuable in this respect. Several types are now available in this country, including Inhal-Aid, InspirEase, Breathancer and Aerochamber. Spacers may be of particular value for administering inhaled corticosteroids by reducing the incidence of oral candidiasis or dysphonia. Beclomethasone, triamcinolone and flunisolide are corticosteroids that can be prescribed for use as aerosols by metered-dose inhaler, as can cromolyn sodium (Intal Spinhaler); the triamcinolone inhaler is available with an attached spacer.

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Oral Rehydration Therapy for Diarrhea

ORAL REHYDRATION THERAPY for diarrhea uses the principle of glucose-facilitated intestinal absorption of sodium and water to rapidly return a child to a euhydrated state. When successful, rehydration can be accomplished in 6 to 12 hours, obviating the need for parenteral therapy. Recent interest in oral rehydration therapy developed because of the need to find an effective, safe and practical treatment of dehydration associated with cholera in areas where parenteral therapy was unavailable. Use of the World Health Organization (WHO) oral rehydrating solution resulted in a dramatic decrease in mortality. Global acceptance of oral rehydration therapy is slowly evolving. Children have a prodigious capacity to absorb sodium-containing fluid at rates exceeding 15 ml per kg per hour. Intestinal sodium absorption can be facilitated in the presence of 2.0% to 2.5% glucose, but the glucose-linked sodium transport system becomes saturated with glucose concentrations greater than 3%, which may result in increased diarrhea due to intestinal hyperosmolarity. Fasting has a negative effect on sodium and water absorption.

Conventional therapy for diarrhea resulting in dehydration is to withhold oral fluids and replace deficits intravenously over 24 hours. Oral intake of fluids is usually reinstituted with small, frequent feedings of clear liquids followed by diluted formula. While effective and relatively safe, this regimen is empirical, expensive and disregards the capacity of the intestine to absorb fluid and electrolytes despite concomitant stool losses.

In contrast, oral rehydration therapy uses glucose to facilitate intestinal salt and water absorption, deficits being replaced over 6 to 12 hours. Sucrose has been substituted in some regimens because of its universal availability and diminished cost. Its efficacy approaches that of glucose despite dependency on intestinal disaccharidases for hydrolysis. Rice powder that contains glycine plus amylose and amylopectin (which can be hydrolyzed to glucose) will significantly lower stool output and duration of diarrhea when compared with the standard 2% glucose solutions. Homemade sugar-salt solutions are not recommended because of the risk of inappropriate reconstitution.

The WHO oral rehydrating solution contains sodium, 90 mEq per liter; potassium, 20 mEq per liter; chloride, 80 mEq per liter; bicarbonate, 30 mEq per liter, and glucose, 111 mmol per liter. The composition of this solution approximates conventional mixtures used to treat moderate dehydration intravenously except in its glucose concentration. The volume of fluid to be given orally or via nasogastric tube in the first six hours is derived from the estimated percent dehydration (50 to 100 ml per kg), maintenance needs (25 ml per kg per six hours) and projected ongoing losses (12 ml per kg per six hours). Two thirds of the total volume is replaced over four hours with the WHO oral rehydrating solution. The final third is given as free water over the next two hours to allow for renal excretion of excess solute. Alternatively, 100 ml per kg of the WHO solution may be given for four hours, followed by 50 ml per kg of water during the next two hours.

Subsequent oral therapy should provide for maintenance fluid and electrolyte requirements and for anticipated ongoing losses. Use of the WHO oral rehydrating solution during this maintenance phase is not recommended. A solution that contains about 30 to 50 mEq per liter sodium, 20 to 30 mEq per liter potassium and 2% glucose should be used for no more than 24 hours. Return to a non-lactose-containing formula should commence within 24 hours. Breast-feeding should be continued throughout the diarrhea.

Traditionally pediatricians have been warned against rapid rehydration, particularly in children with hypernatremia, to avoid seizures due to intracellular influx of water. Although oral rehydration therapy results in a more rapid fall in serum sodium levels when compared with intravenous therapy, the incidence of seizures is not increased. In one study, the risk of seizures was related to the initial serum sodium concentration rather than to the rate of fall in serum sodium concentration. In addition, the occasional hyponatremia measured after oral rehydration therapy seems to be clinically insignificant. In children with hypovolemic shock, this therapy should only be used after adequate volume expansion with intravenous fluids and when the child is alert enough to cooperate with the regimen. Vomiting is not a contraindication to oral rehydration therapy, as rapid restoration of volume seems to diminish vomiting. Failure can be anticipated if the loss exceeds 10 ml per kg per hour and in children with paralytic ileus, in those with known glucose or sucrose intolerance or when purge rates exceed 10 ml per kg per hour.

Despite these possible obstacles, oral rehydration therapy obviates the need for the intravenous administration of fluids in 75% to 95% of children treated for dehydration. Appropriate use and careful monitoring will assure the safety of oral rehydration, which represents a physiologic, noninvasive and potentially cost-effective alternative approach to the conventional management of diarrhea in childhood.

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Surfactant Treatment of the Respiratory Distress Syndrome

SOON AFTER the identification of dipalmitoylphosphatidylcholine as the principal compound in pulmonary surfactant and the recognition in 1959 that infants who died of the respiratory distress syndrome had abnormal surface properties of the lungs, aerosols of this compound were tried unsuccessfully as treatment for this disorder. In the 1970s, however, a sound scientific basis for treatment with natural surfactant was established in preterm animals. In 1980 the results of the first uncontrolled trial of the use of surfactant prepared from beef lung were published. Since then 15 studies have been published, of which 6 have been controlled, randomized clinical trials. While many of these have shown remarkable responses to surfactant, others have shown no effects, depending on the surfactant chosen for the studies.

Natural pulmonary surfactant is a complex mixture of phospholipids, neutral lipids and at least two classes of surfactant-specific proteins. Surfactant is present in the airways and alveoli as aggregates of various sizes, the most surface active being the largest. These large surfactant aggregates will rapidly absorb to and spread on an air-water interface to establish an equilibrium surface tension of about 25 dynes per cm. On dynamic compression of the surface film, surfactant will lower the surface tension to values less than 10 dynes per cm. These surface properties can be reproduced using carefully resuspended lipid extracts of natural surfactant that contain less than 1% protein. The technique of resuspension is critical to surface behavior, as the composition of a surfactant is less important than the aggregate form of the lipids in suspension. Further, synthetic lipid surfactants can have in vitro properties similar to natural surfactant, yet be inactive in vivo. A surfactant for clinical use is not a traditional single-component pharmaceutical; rather, surfactant is a mixture of compounds whose surface physical properties in vitro may not be sufficient for in vitro function. Responses to a surfactant may be predicted only from the effects on surfactant-deficient premature lungs.

Based on sound experiments in animals, two strategies for clinical trials have been used. In the initial pilot trial, ventilator-dependent infants with severe respiratory distress syndrome were treated with tracheal instillation of suspensions of surfactant in saline. In a number of subsequent trials, workers have tried to prevent the respiratory distress syndrome by treating at-risk infants with surfactant in the delivery room. Infants treated with synthetic surfactants have no immediate improvement in lung function. In contrast, infants treated with animal or human surfactants may have immediate im-